Chemical Translations

DR. S. EDMUND BERGER | 298 GRAYTON ROAD, TONAWANDA, N.Y . 14150 | VOICE (716) 832-7316 FAX (716) 833-1970

CERTIFICATE OF ACCURACY

State of New York
} ss.
County of Erie

TRANSLATION FROM *German*

On this day, I **S. Edmund Berger** state:

that I am a professional translator of the *German* and English languages, doing business as *Chemical Translations*, 298 Grayton Road, Tonawanda, NY 14150;

that I am thoroughly familiar with these languages and have carefully made and/or verified the attached translation from the original document

New PCT Application
PCT/EP/00/02513
Inv.: Schwarz, S., et al.
Ref.: 1815

EQUILENIN DERIVATIVES, METHODS FOR PRODUCING THE SAME AND MEDICAMENTS CONTAINING THEM

as submitted to me in the

German language;

and that the said translation is a true, complete and correct English version of such original to the best of my knowledge and belief.

S. Edmund Berger
Nov. 10, 2001

Equilenin Derivatives, Methods for Producing the Same and Medicaments Containing Them

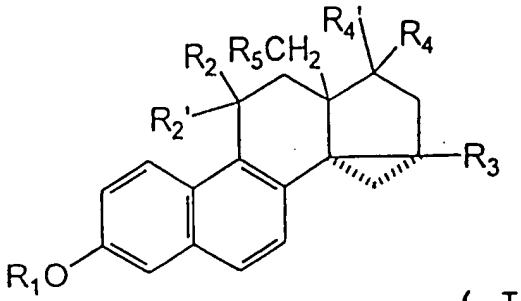
The present invention relates to novel equilenin derivatives, methods for producing the same and medicaments containing them.

Equilenin itself is an estrogenic steroid obtainable from the urine of pregnant mares.

The novel equilenin derivatives of the invention have an oxygen function on carbon atom 11 and an α-methylene bridge between carbon atoms 14 and 15. Equilenin derivatives with an oxygen function on carbon atom 11 are known. Thus, the racemic 11-oxoequilenin methyl ether was obtained by total synthesis [Tetrahedron Lett. 2763 (1967); Austr. J. Chem. 23, 547 (1970); J. Org. Chem. 39, 2193 (1974)]. A total synthetic route was also used to obtain racemic 11-oxo-3-methoxyestra-1,3,5(10),-6,8,14-hexaen-17β-ylcarboxylic acid [Tetrahedron Lett. 479 (1968)]. 14α,17α-Bridged equilenin derivatives with an 11-oxygen function were obtained by partial synthesis. The introduction of the 11-oxygen function into the molecule was achieved with Ce(IV) ammonium nitrate [Tetrahedron Lett. 35, 8599 (1994)]. Equilenin derivatives with an α- or β-methylene bridge between carbon atoms 14 and 15 have also been prepared by partial synthesis whereby the B ring was dehydrogenated with dichlorodicyanobenzoquinone (DDQ) [Tetrahedron Lett. 35, 2329 (1994)].

The object of the present invention is to provide novel equilenin derivatives and a method for producing the same.

According to the invention, this objective is reached by forming equilenin derivatives of general formula (I)



(I)

wherein

R_1 denotes a hydrogen atom, a C_1-C_6-alkyl group, a C_1-C_6-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' denotes a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_6-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group

and
R_6 denotes a hydrogen atom or a methyl group.
According to the invention, R_6 is preferably a hydrogen atom.

According to the invention, particularly preferred equilenin derivatives are, for example:

1) 14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
2) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate,
3) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl propionate,
4) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17β-yl decanoate,
5) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17-one,
6) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17β-diyl diacetate,
7) 15β-methyl-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
8) 11β-fluoro-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,17β-diol,
9) 3,17β-dihydroxy-14α,15α-methylene-1,3,5(10),6,8-pentaen-11-one,
10) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate,
11) 3-methoxy-14α,15α-methylene-11-oxoestra-1,3,5(10),6,8-pentaen-17α-yl acetate,
12) 11β-hydroxy-17,17-difluoromethylene-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate, and
13) 14α,15α-17,17-bis-methylenestra-1,3,5(10),6,8-pentaene-3,11α-diol.

For purposes of the present invention, "C_1-C_6-alkyl" means a branched or straight-chain alkyl group. Examples are the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert.butyl, n-pentyl or isopentyl groups.

For purposes of the present patent application, "C_{1-5}-acyl or C_{1-11}-acyl" means a radical of a straight-chain or branched alkanecarboxylic acid with 1 to 5 or with 1 to 11 carbon atoms, for example a radical of formic, acetic, propionic, butanoic, isobutanoic, heptanoic or undecanoic acid.

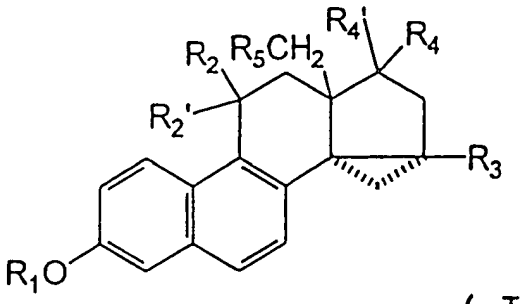
For purposes of the present invention, "halogen" means an atom of fluorine, chlorine, bromine or iodine.

The equilenin derivatives of the invention are new. Thus far, they have neither been prepared nor have their properties been described. The equilenin derivatives of the invention exhibit antioxidative activity and minor systemic hormonal action. The antioxidative activity was determined by, among other things, inhibition of iron(II)-catalyzed lipid peroxidation in synaptosomal membrane fractions of rats, by inhibition of copper(II) sulfate-induced LDL cholesterol oxidation and by inhibition of xanthine oxidase and of various other monooxygenases. The systemic estrogen action was evaluated by the Allen-Doisy test in rats. The spectrum of activity of the equilenin derivatives of the invention makes them potentially suitable for therapeutic use in all those cases in which oxygen radicals are in a causal

relationship with diseases of organs or tissues, for example in brain or spinal column injuries, states of shock, emphysema, acute respiratory distress syndrome [ARDS], ageing processes, tissue injuries after a myocardial infarction, injuries caused by intoxication or irradiation, burns and transplantation-related immune reactions, such as organ injuries in the reperfusion phase following transplantations, in spinal trauma, stroke, arteriosclerosis, ischemia, chronic-degenerative diseases of the CNS, senile dementia of the Alzheimer type (SDAT), asthma, muscular dystrophy and degenerative neurological diseases, among others, in the form of CNS intoxication or degeneration states. A preferred field of application is geroprophylaxis in women and - because the compounds of the invention exert only minor feminization action - also in men.

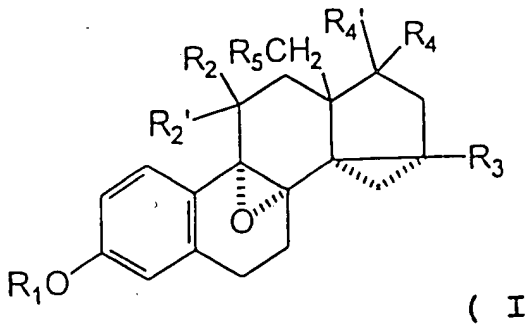
The compounds of the invention can be administered orally as well as parenterally. For oral administration, prodrugs in the form of carboxylate esters are particularly advantageous, because they provide active substance levels that remain constant for a long time.

Another object of the present invention is a method for producing the equilenin derivatives of the invention of general formula (I)



(I)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the afore-indicated meaning, by making a compound of general formula (II)

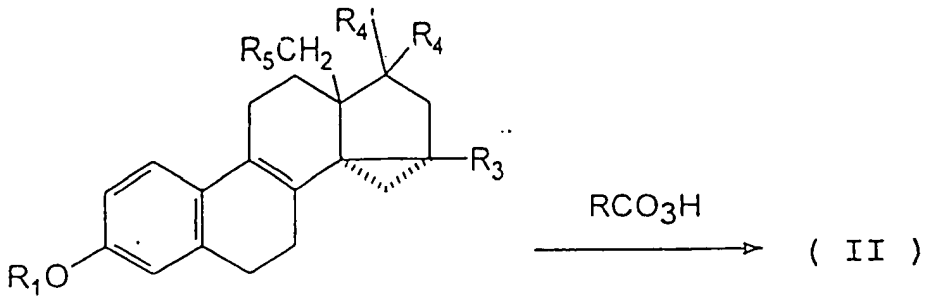


(II)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the afore-indicated meaning, react with diphosphorus tetraiodide in the presence of pyridine, and then converting the resulting compound into a compound of general formula (I) in a manner which in itself is known.

It is known that diphosphorus tetraiodide reacts with epoxides and alcohols. Thus, epoxides can be reduced to olefins with diphosphorus tetraiodide [Synthesis 905 (1978); Nouv. J. Chem. 3, 745 (1979)]. Alcohols react with diphosphorus tetraiodide forming iodides [Tetrahedron Letters 1801 (1979); J.C.S. Chem. Commun. 229 (1983)] or with elimination to give olefins [Helv. Chim. Acta 11, 106 (1928)] or to give cumulenes [Ber. 71, 1899 (1938)]; ibid. 85, 386 (1952); ibid. 87, 598 (1954); J.C.S. Chem. Commun. 885 (1975)]. An outstanding feature of the method of the invention is that the action of diphosphorus tetraiodide on compounds of general formula (II) eliminates the 8,9-oxido group and at the same time introduces an additional double bond between carbon atoms 6 and 7. In this manner, it is possible to produce the equilenin derivatives of the invention having general formula (I) from compounds of general formula II in one step, and to avoid an additional reaction step to introduce the 6,7-double bond [Tetrahedron Letters 35, 2329 (1994)]. Another outstanding feature of the method of the invention - provided that compounds of general formula II are used wherein R_2 denotes hydrogen and R_2' stands for a hydroxyl group - is that neither elimination of the unprotected hydroxyl group to the corresponding olefin nor substitution of the hydroxyl group with iodine takes place. The course and the high selectivity of the method of the invention are surprising and could not have been predicted by someone skilled in the art.

Compounds of general formula II can be obtained from compounds of general formula III, wherein R_1 and R_3 to R_5 have the same meaning as indicated for the compounds of formula II, by treating said compounds of formula III with excess peroxycarboxylic acid

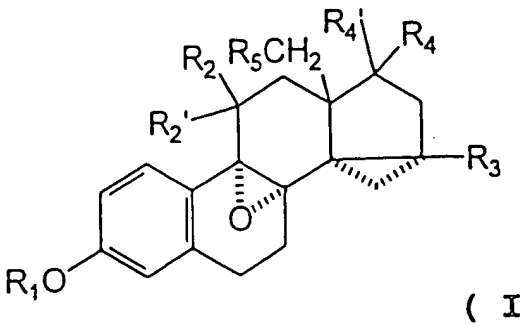


(III) (II)

Optionally, the equilenin structure of the derivatives obtained according to the invention can be further modified by methods that in themselves are known. For example, it is possible to subject compounds of general formula I, wherein R_2' denotes an α-hydroxyl group and R_2 a β-hydrogen, to oxidation with activated dimethyl sulfoxide in a known manner to form the corresponding 11-oxo compounds which can then be reduced with a complex metal hydride to form the corresponding 11β-hydroxy derivatives. Alternatively, the reaction of compounds of general formula I, wherein R_2' denotes an α-hydroxyl group and R_2 a β-hydrogen, with diethylaminosulfur trifluoride (DAST) gives compounds with an 11β-fluoro group. Compounds of general formula I, wherein R_4' denotes a C_1-C_6-alkyl group, can be converted into the free phenols with boron tribromide or diisobutylaluminum hydride in a manner which in itself is known. Compounds of general formula I, wherein R_4' denotes an α-hydroxyl group and R_4 a β-

hydrogen, can be oxidized with activated dimethyl sulfoxide in a manner which in itself is known to give the corresponding 17-oxosteroids, which upon reduction with borane or an oxazaborolidine afford 17β-hydroxy compounds.

The cyclopropano steroids of general formula II



(II)

wherein

R_1 denotes a hydrogen atom, a C_1-C_5-alkyl group, a C_1-C_5-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_5-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group, or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group and

R_5 denotes a hydrogen atom or a methyl group,

are new and have previously not been described.

Particularly preferred are, for example, the following cyclopropano steroids:

1) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-ol,
2) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
3) 3-methoxy-14α,15α-methylene-8α,9α-oxido-18a-homoestra-1,3,5(10)-trien-17α-yl propionate,
4) 14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-3,17α-diyl diacetate,
5) 3-methoxy-15β-methyl-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17β-ol,
6) 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
7) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate and
8) 3-methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylenestra-1,3,5(10)-trien-17β-yl acetate.

These compounds represent novel intermediates for obtaining the equilenin derivatives of the invention and thus constitute a further object of the present invention.

The object of the present invention are also medicaments for oral, transdermal, rectal, subcutaneous, intravenous or intramuscular administration which contain a compound of general formula I as the active ingredient besides common carriers or diluents.

The medicaments of the invention are prepared in the known manner with an appropriate active substance content using common solid or liquid carriers or diluents and the commonly employed pharmaceutical auxiliary agents, depending on the route of administration desired. The preferred preparations are dosage forms suitable for oral administration. Such dosage forms are, for example, tablets, film-coated tablets, sugar-coated tablets, capsules, pills, powders, solutions, suspensions or depot forms.

Naturally, parenteral preparations such as solutions for injection are also suitable. Other suitable preparations are, for example, suppositories.

Accordingly, tablets can be obtained, for example, by mixing the active substance with known auxiliary agents, for example with an inert diluent such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, a disintegrant such as corn starch or alginic acid, a binder such as starch or gelatin, a lubricant such as magnesium stearate or talc and/or an agent for producing a depot effect, such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can consist of several layers.

Coated tablets can be prepared by coating cores, prepared in the same manner as the tablets, with substances commonly used for tablet coating, for example polyvinylpyrrolidone, shellac, gum arabic, talc, titanium dioxide or sugar. The coating of the coated tablet can also consist of several layers obtained with the aid of auxiliary agents mentioned hereinabove in relation to the tablets.

Solutions or suspensions comprising the active substance of the invention can additionally contain a taste-improving agent such as saccharin, cyclamate or sugar, and also, for example, a flavoring agent such as vanillin or orange extract. They can also contain a suspension aid such as sodium carboxymethylcellulose or a preservative such as a p-hydroxybenzoate. Capsules containing an active substance can be prepared, for example, by mixing the active substance with an inert carrier, such as lactose or sorbitol, and encapsulating the mixture in gelatin capsules.

Suitable suppositories can be prepared, for example, by mixing the active substance with a carrier suitable for this purpose, for example with a neutral fat or polyethylene glycol or a derivative thereof.

A suitable dosage form is, for example, active substance-containing adhesive tape. Such systems are known.

The following examples will explain the invention.

EXAMPLE 1

11α-Hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate from 3-methoxy-14α,15α-methylenestra-1,3,5(10),8-tetraen-17α-yl acetate

Peroxyacetic acid (32%, 5.5 mL) was added at room temperature to a solution of the tetraene steroid (3.5 g) in dichloromethane (120 mL). The reaction mixture was allowed to stand overnight at room temperature. The solution was then treated in succession with aqueous sodium thiosulfate solution (20%), saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried over magnesium sulfate and concentrated under vacuum. The residue was subjected to flash chromatography on silica gel (eluent: cyclohexane-ethyl acetate, 3:2 v/v). Crystallization from acetone/n-hexane gave the title compound.

M.p. 159-162.5 °C. ^{1}H-NMR ($CDCl_3$/TMS[1]): 7.80 (d, J = 8.8 Hz, H-1), 6.79 (dd, J = 8.8, 2.8 Hz, H-2), 6.65 (d, J = 2.8 Hz, H-4), 4.93 (q, J = 7.9 Hz, H-11), 4.78 (d, J = 5.9 Hz, H-17), 3.80 (s, -OCH_3), 2.03 (s, -OOC-CH_3), 1.11 (dd, J = 5.4, 3.2 Hz, 14,15-CH_2-), 0.88 (s, H-18), 0.69 (ddd, J = 6.6, 5.4, 1.7 Hz, 14,15-CH_2-). MS (m/z): 354 (M^+), 336, 294, 277, 261.

EXAMPLE 2

3-Methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate from 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate

Acetic anhydride (4 mL) and dimethylaminopyridine (0.04 g) were added at room temperature to a solution of the 11α-hydroxy steroid (0.4 g) in pyridine (4 mL). The mixture was stirred at room temperature for 3 hours after which it was poured into ice water. The resulting precipitate was filtered off, washed neutral with water and air-dried. Flash chromatography on silica gel (eluent: cyclohexane-ethyl acetate, 7:3 v/v) gave the title compound.

M.p. 151-154 °C. ^{1}H-NMR ($CDCl_3$/TMS): 7.80 (d, J = 8.8 Hz, H-1), 6.79 (dd, J = 8.8, 2.8 Hz, H-2), 6.65 (d, J = 2.8 Hz, H-4), 4.93 (q, J = 7.9 Hz, H-11), 4.78 (d, J = 5.9 Hz, H-17), 3.80 (s, -OCH_3), 2.03 (s, -OOC-CH_3), 1.11 (dd, J = 5.4, 3.2 Hz, 14,15-CH_2-), 0.88 (s, H-18), 0.69 (ddd, J = 6.6, 5.4, 1.7 Hz, 14,15 -CH_2-). MS (m/z): 354 (M^+) 336, 294, 277, 261.

---

[1] TMS = tetramethylsilane - Translator

EXAMPLE 3

3-Methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate from
3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate

A solution consisting of the steroid diacetate (0.1 g), chloroform (2.4 mL) and pyridine (0.24 mL) was added dropwise to a stirred suspension of diphosphorus tetraiodide (0.14 g) in chloroform (2.4 mL) under argon protection. The mixture was then heated at reflux for 13 hours with agitation. Water was added, the organic phase was separated, and the aqueous phase was extracted exhaustively with chloroform. The combined organic phases were washed in succession with hydrochloric acid (1 N), water, saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution and then dried over magnesium sulfate and concentrated under vacuum. The residue was subjected to flash chromatography which gave the title compound.

^{1}H-NMR ($CDCl_3$/TMS): 7.66 (d, J = 8.8 Hz, H-6,7), 7.58 (d, J = 9.5 Hz, H-1), 7.17 (dd, J = 9.5, 2.8 Hz, H-2), 7.13 (d, J = 2.8 Hz, H-4), 6.85 (d, J = 8.8 Hz, H-6,7), 6.78 (q, J = 8.1 Hz, H-11), 4.98 (d, J = 6.1 Hz, H-17), 3.92 (s, -OCH_3), 2.11 (s, -OOC-CH_3), 2.09 (s, -OOC-CH_3), 1.46 (dd, J = 4.9, 3.2 Hz, 14,15-CH_2-), 0.97 (s, H-18), 0.57 (ddd, J = 8.2, 4.9, 1.7 Hz, 14,15 -CH_2-). MS (m/z): 394 (M^+), 334, 274, 259.

EXAMPLE 4

11α-Hydroxy-3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17α-yl acetate from
11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate

As in Example 3, the 11-hydroxy compound was treated with diphosphorus tetraiodide, which gave the title compound.

^{1}H-NMR ($CDCl_3$/TMS): 8.26 (d, J = 9.4 Hz, H-1), 7.62 (d, J = 8.3 Hz, H-6,7), 7.22 (dd, J = 9.4, 2.7 Hz, H-2), 7.12 (d, J = 2.7 Hz, H-4), 6.83 (d, J = 8.3 Hz, H-6,7), 5.68 (q, J = 7.7 Hz, H-11), 4.99 (d, J = 6.3 Hz, H-17), 3.92 (s, -OCH_3), 2.10 (s, -OOC-CH_3), 0.93 (s, H-18), 0.57 (ddd, J = 7.6, 4.8, 1.6 Hz, 14,15-CH_2-). MS (m/z): 370 (M^+), 353, 310, 292, 277, 267.